American Journal of Medical Genetics 92:7–12 (2000)

Two Novel Fibrillin-2 Mutations in Congenital Contractural Arachnodactyly

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Congenital contractural arachnodactyly (CCA) is an autosomal dominant connective tissue disorder, comprising marfanoid habitus, flexion contractures, severe kyphoscoliosis, abnormal pinnae, and muscular hypoplasia. It is now known that mutations in the gene encoding fibrillin-2 cause CCA. Interestingly, mutations described to date cluster in the fibrillin-2 region homologous to the so-called neonatal Marfan syndrome region of fibrillin-1. Thus, it has been hypothesized that the relative infrequency of CCA compared with the Marfan syndrome is due to the limited region of the gene targeted for mutations. In support of the above hypothesis, we report here the finding of two additional FBN2 mutations in CCA, C1141F (exon 26) and C1252W (exon 29). In addition, a new 3′ UTR polymorphism is also described. Am. J. Med. Genet. 92:7–12, 2000.

KEY WORDS: Beal's syndrome; congenital contractural arachnodactyly; mutation; fibrillin-2; polymorphism

INTRODUCTION

The long quest to identify the genetic basis of the Marfan syndrome (MFS) ended in 1991 with the discovery of the fibrillin gene on chromosome 15 (Fib15/FBN1)[Lee et al., 1991]. Serendipitously, a second fibrillin gene that mapped to chromosome 5 was also identified (Fib5/FBN2) [Lee et al., 1991]. The complete amino acid sequences of FBN1 and FBN2 have now been published [Zhang et al., 1994; Pereira et al., 1993]. Genetic linkage analyses linked FBN2 to congenital contractural arachnodactyly (CCA) [Tsipouras et al., 1992; Lee et al., 1991]. The phenotype of CCA overlaps that of MFS [Hecht and Beals, 1972; Epstein et al., 1968; Beals and Hecht, 1971]. CCA is an autosomal dominant trait and sporadic cases are also observed [Lowry and Guichon, 1972; Bjerkreim et al., 1976; Beals and Hecht, 1971]. The incidence of CCA is not known but appears to be less frequent than the Marfan syndrome. Individuals with CCA typically have a marfanoid habitus, flexion contractures, severe kyphoscoliosis, abnormal pinnae, and muscular hypoplasia. Unlike MFS, CCA is associated with a normal lifespan.

Numerous FBN1 mutations have been identified. These result in a wide range of findings: relatively mild skeletal abnormalities [Milewicz et al., 1995], ectopia lentis [Kainulainen et al., 1994; Lonnqvist et al., 1994], late onset aortic aneurysms [Francke et al., 1995], neonatal Marfan syndrome [Wang et al., 1995, 1997; Milewicz and Duvic, 1994; Kainulainen et al., 1994], and classical Marfan syndrome [for review, see Dietz and Pyeritz, 1995]. However, to date, only nine FBN2 mutations have been identified in patients with CCA [Babcock et al., 1998; Park et al., 1998; Maslen et al., 1997; Putnam et al., 1995, 1997; Wang et al., 1996]. Interestingly, all of these FBN2 mutations occur in a rather limited region of FBN2. The analogous region in FBN1 is the so-called "neonatal Marfan region" where most mutations that cause the most severe form of the Marfan syndrome are found [Kainulainen et al., 1994]. Here we describe two novel cysteine mutations: a T to G transversion at position 3756, resulting in a Cys 1252 Trp change, and a G to T transversion at position 3422, resulting in a Cys 1141 Phe substitution. Both of these mutations are found within the exon 24 to 34 region. In addition, a 3′ UTR polymorphism was de-

Grant sponsor: American Heart Association, Heartland Affiliate; Grant number: 9807991S; Grant sponsor: March of Dimes Birth Defects Foundation; Grant number: FY98-0522; Grant sponsor: National Marfan Foundation, USA; Grant sponsor: American Heart Association, National Center.

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Received 19 July 1999; Accepted 26 January 2000

tected in one of these patients. Population studies showed the presence of this polymorphism in 9 of 150 chromosomes (6.0%).

MATERIALS AND METHODS

Patient Samples

Patient 1 (CF1347) is an 8-year-old girl, born to non-consanguineous parents of French Canadian origin (Figs. 1, 2). At the time of her birth, the mother was 36 years old and the father 37. Delivery was by repeat cesarean section. The birth weight was 3,050 g, birth length was 49 cm, and birth head was circumference 32.5 cm. Apgar scores were 8 and 9 at 1 and 5 min, respectively.

During this pregnancy, the mother had some vaginal bleeding in the first trimester and hypertension during the last trimester; otherwise the pregnancy was uneventful. An older sister and an older brother are healthy. Another sister, born 5 years earlier, died at the age of 1 year of congenital cardiac anomalies. The family history is otherwise non-contributory.

At the age of 2 months, during a genetics consultation, she was found to have a cleft palate, low-set ears with abnormal folds of the pinnae, orbital hypertelorism, micrognathia, single palmar creases bilaterally, and limited joint movements at the elbows, knees, and hips. Based on these findings, the diagnosis of CCA was made.

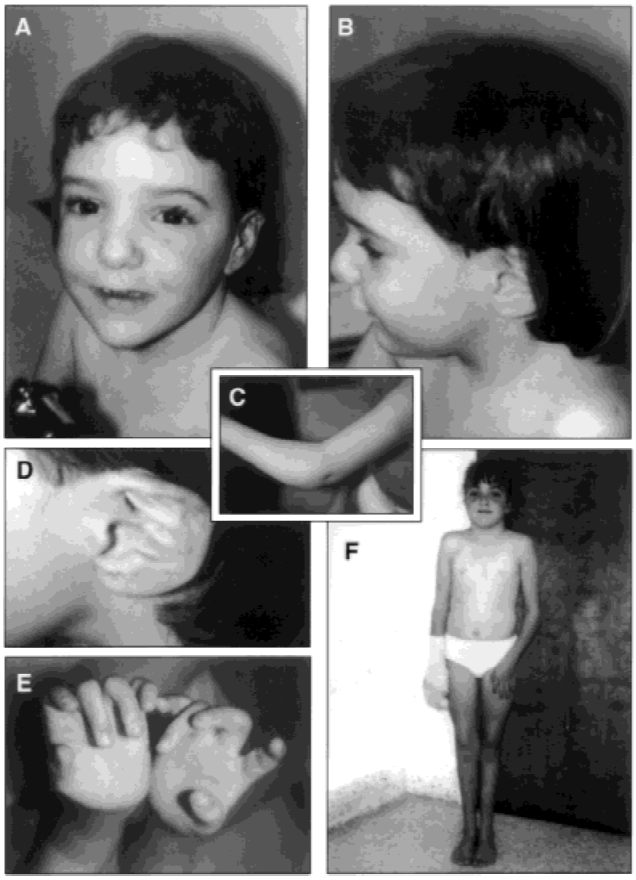

Fig. 1. Patient CF 1347. **A:** Face at 3 years. **B:** Profile at 3 years. **C:** Left elbow at 3 years (note contracture). **D:** Left ear at 3 years (note crumpled upper pinna). **E:** Hands at 3 years (note arachnodactyly and camptodactyly). **F:** Total body (note bandaged right hand after surgery for the camptodactyly and also the thin legs below the knees.

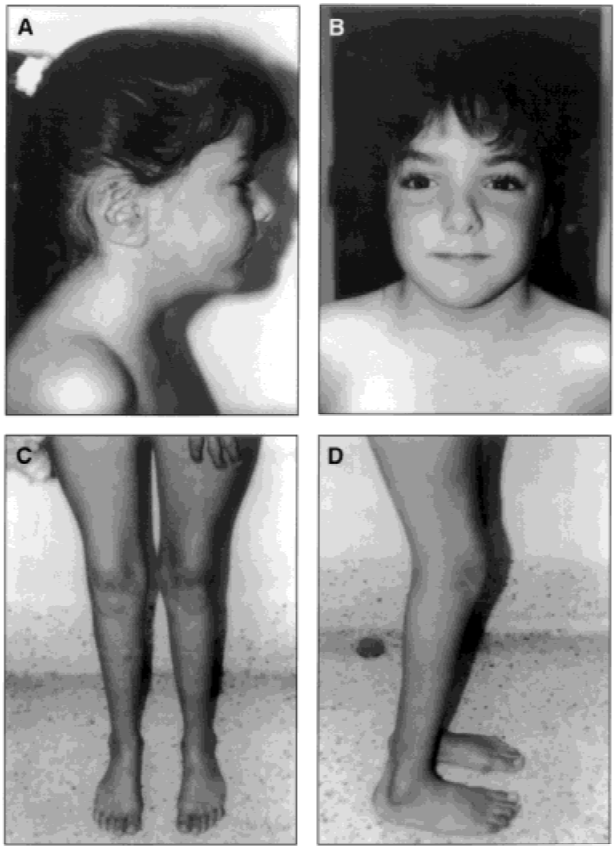

Fig. 2. Patient CF 1347 at 8 years. **A:** Profile (note crumpled upper pinna). **B:** Face. **C:** Anterior aspect of lower extremities. (Note thin legs below knees). **D:** Lateral aspect of lower extremities.

Results of blood karyotype, renal echography, radiography of the chest and abdomen, and an electroencephalography were normal. She had been operated on for her cleft palate at the age of 1 year. Her psychomotor development and school performance are normal.

At 8 years, her height was 124 cm (around the 45th centile), her weight was 23 kg (~30th centile), and her head circumference was 51.5 cm (50th centile). The palate is high and narrow arched. The pinnae are "crumpled." There is a mid-thoracic kyphoscoliosis. There is restriction to the extension of the thumbs at the metacarpophalangeal joint. The extension at the distal interphalangeal joints of the first to fourth fingers is also limited bilaterally. Mild pterygia are noted at the fingers and elbows, limiting their extension. Muscle mass below the knees is small with slight limitation of extension at both knees. A 2.9 × 2 cm café-au-lait spot is present on the right arm laterally and another one (2.5 × 0.8 cm) at the left lumbar paravertebral area. The rest of the physical findings, including a cardiac findings, are normal.

Patient 2 (CF1449) is a 14 7/12-year-old girl with tall stature, slender body habitus, arachnodactyly, camptodatyly, and progressive kyphoscoliosis. She had mild

mental retardation and mild spasticity. The patient was born to her gravida 4 para 3 mother. Delivery was at term. She was first evaluated in the medical genetics clinic at age 3 4/12 years. She walked independently at age 18 months. At 3 4/12 years she had only four spoken words, although receptive language was better than expressive language. IQ testing documented a verbal score of 70, performance score was 61, and full scale IQ was 65.

Radiographs of the spine obtained at 2 ½ years documented anterior beaking of the vertebrae, mild scoliosis, and loss of lumbar lordosis. At age 6 ½ years, she began wearing a body brace for progressive scoliosis. In a 10 month period, between 13 and 14 years, she experience painless progression of her right thoracic scoliosis between T5 and T11 from 52 to 65°. There was no related neurological deficit. At 14 years of age, she underwent posterior spinal instrumental fusion from T4 to T12 with Isola hooks; 3/16-inch instrumentation was used because of "minimal soft tissue." The postoperative residual right convex curve remained stable with the apex at T8. Subsequent radiographs showed abnormal iliac bones and bilateral coxa valga.

At 2 ½ years, her height was at the 50 to 75th centile but increased to the 95th centile by 4 3/12 years. At 14 7/12 years, her height was 161.6 cm (50th centile), weight was 30.7 kg (< 5th centile). and her OFC was 51 cm (< 2nd centile).

Physical examinations between the ages of 2 and 14 years documented a round and flat face with a flat nasal root and upturned nose, inner canthal distance of 2.8 cm and outer canthal distance 8.2 cm, no iridodenesis, and slightly thickened helices of the ears, which were not crumpled. Both ears were 5.2 cm long. Her palate was slightly narrow but not vaulted. Her teeth were normally positioned without dental crowding. She had no heart defects. Her arms were long and slender with decreased muscle mass. She lacked 15° of extension at the elbows but had normal supination and pronation of her forearms. Her fingers were long and slender with prominence of the joints. On the right hand, she had marked fifth finger camptodactyly and mild flexion contractures of the other three digits but not the thumb. On the left hand, she had mild contractures of the index and middle finger and more significant contractures of the ring and little fingers. She had slender legs with reduced muscle mass, particularly in the calves. She had a full range of motion at her knees. Her ankles were hypermobile and her feet were long, narrow, and pronated. Her toes were long and slender without contractures. She had a stiff-legged gait with severe intoeing. Her balance and strength were normal, but her deep tendon reflexes were 3 plus at the biceps, triceps, brachioradialis, and knees. She had unsustained clonus at the ankles. She had no Babinski responses. Skin was normal without unusual pigmentation, striae, or laxity.

Chromosomes were normal (46,XX). A urine metabolic screen at 6½ years of age showed no homocysteine but did show increased amounts of taurine. A 3 mm punch skin biopsy was obtained for fibrillin studies from her arm at age 14 ½ years.

The patient had two older sibs and one younger brother. An older sib was also said to be developmentally delayed. The mother was never evaluated in the genetics clinic but also was said to be developmentally delayed. The parents were not known to be related to each other. There were no other individuals in the family known or suspected to have similar medical problems.

Extraction of Nucleic Acids

DNA. Extraction of DNA from dermal fibroblasts was carried out by incubating 5×10^6 cells in 200 μl of lysis buffer [10 mM Tris HCl (pH 8.0), 2 mM EDTA, 10 mM NaCl, 5% sodium dodecyl sulfate (SDS), and 200 μg/ml Proteinase K] at 55°C for 16 hr [Sambrook et al., 1989]. In all extractions, the aqueous DNA was recovered by using phenol/chloroform extractions and isopropanol precipitation. The extracted DNA was suspended in a 10 mM Tris HCl (pH 7.4), 1 mM EDTA (pH 8.0) solution and concentration and purity were assessed spectrophotometrically.

RNA. RNA was extracted from dermal fibroblasts by using established techniques [Chomczynski and Sacchi, 1987]. Briefly, cells were lysed in situ in a guanidine thiocyanate buffer containing β-mercaptoethanol. RNA was extracted with phenol/chloroform, precipitated with ethanol, and stored at –80°C prior to use.

cDNA Production

Production of cDNA from RNA was performed by using a commercially available kit (Amersham, Arlington Heights, IL) according to the manufacturer's protocol.

Polymerase Chain Reaction (PCR)

Amplification of the patients' fibroblast cDNA was performed using 45 pairs of overlapping primers to cover the entire approximately 10 kb coding region. Following PCR amplification, the amplicons were subjected to heteroduplex analyses (see below). Heteroduplex bands for patient CF1347 were found by using primers A and B and patient CF1449 heteroduplex bands were found by using primers C and D (Table I). A heteroduplex band was also found in two unrelated patients by using primers E and F. Amplification was performed for 30 cycles: denaturation at 94°C for 1 min, annealing for 2 min (temperature for each primer pair is indicated in Table I), and extension at 72°C for 30 sec.

Heteroduplex Analyses

Amplified products were screened for the presence of possible mutations by using Mutation Detection Enhancement (MDE) (FMC Corp., Rockland, ME) gels. In order to maximize the formation of heteroduplexes, Ten microliters of PCR product was mixed with 2 μl of gel loading buffer (50% sucrose, 0.6% xylene cyanol, and 0.6% bromophenol blue) and incubated at 95°C/3 min, 75°C/5 min, 55°C/5 min, and 37°C for at least 5 min and until all samples were loaded on the gel. Samples were resolved on 0.5× MDE gels at 800 V for approximately 5 hr, according to manufacturer's protocol. After electrophoresis, gels were stained in a solu-

TABLE I. Sequence of FBN2 cNDA Oligonucleotide Primers and the Pair's Respective Annealing Temperature for PCR*

Primer	Sequence	Annealing temperature
A Sense	5′ TCT CCT GAC CTC TGT GGC 3′	55°C
B Anti-Sense	5′ TCA CAC ATT TTC CAT TTC TGC 3′	
C Sense	5′ TAT GAA GTA AAA AGC GAG AAC 3′	53°C
D Anti-Sense	5′ ATC GTC TTT GGG GCA CAG 3′	
E Sense	5′ AGA GCA ATG AGG ATG ACT AC 3′	55°C
F Anti-Sense	5′ CCA CGG TTG CCT TTG AGC 3′	

*Amplification conditions and patient specificities are noted in the text.

tion of 0.6× TBE, containing 1 μg/ml ethidium bromide and DNA visualized under UV light.

Nucleotide Sequencing

All PCR products were gel purified and sequenced directly as previously described [Wang et al., 1996] or sequenced by using an automated sequencer (Applied Biosystems, Foster City, CA; Model 372A) in the core sequencing laboratory of the Eppley Institute of the University of Nebraska Medical Center. Amplification primers were used as sequencing primers as well. Mutations were confirmed by sequencing genomic DNA.

RESULTS

Heteroduplex analyses of PCR amplifications of 45 overlapping FBN2 cDNA primer pairs showed only one occurrence of heteroduplex formation for each of patients CF1347 and CF1449. The heteroduplex changes for patients CF1347 and CF1449 were seen when primer pairs A/B and C/D were used, respectively (Table I). Direct sequencing of the PCR products showed cysteine substitutions in one FBN2 allele in each patient. Patient CF1347′s mutation was in exon 26, a G3422T transversion that resulted in a C1141F amino acid substitution. Neither of her parents harbored the same change. Thus, the mutation was a de novo event. The mutation in patient CF1449 was in exon 29, a T3756G transversion that resulted in a C1252W amino acid substitution. Her parents were unavailable for testing. Both mutations were confirmed in analysis of genomic DNA. The position of the mutations along a schematic of the domain organization of fibrillin-2 is shown in Figure 3.

While screening samples for FBN2 mutations, a heteroduplex change, using primer pair E/F (Table I), was found in two unrelated patients. Sequencing analysis showed that this was a three base deletion of nucleotides 8830 to 8832 in the 3′ untranslated region. Population studies of 75 unrelated individuals [both CCA

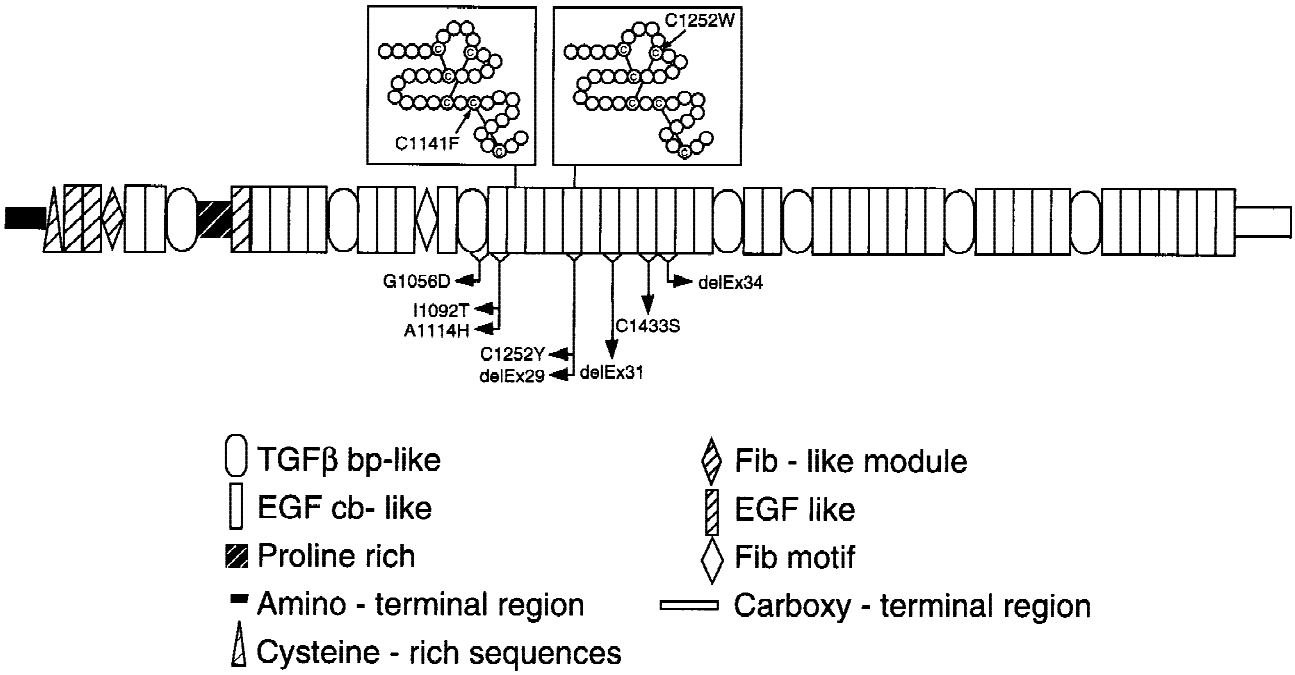

Fig. 3. Diagram of fibrillin-2 domain organization. The mutations in CCA patients previously identified are shown below the schematic, while those reported here are shown within the EGF-like domain above. The peptide motifs are identified below the schematic.

patients (2/15) and unaffected controls (7/60)] showed that 9 of 150 chromosomes (6.0%) contained that polymorphic variant.

DISCUSSION

It is as yet unclear why mutations in FBN1, that cause MFS and related disorders, appear to occur much more frequently than those in FBN2, even though the primary structure of the coding regions of the two genes are highly homologous. In part, it has been recently hypothesized, the difference may be due to the limited region of FBN2 in which CCA mutations are found [Park et al., 1998]. In addition, the usually earlier expression of FBN2 [Mariencheck et al., 1995; Zhang et al., 1995] allows speculation that its importance in development is such that perturbations in fibrillin-2 are poorly tolerated by a developing organism. Our recent expansion of the CCA phenotype to include a severe/lethal form [Wang et al., 1996] supports this possibility. Furthermore, the spectrum of fibrillin-2 disease may continue to expand to include some idiopathic cardiac septal defects, for example, so that the mutation rates of the gamut of FBN1 and FBN2 microfibrillopathies will be similar. However, at present it appears that the systemic manifestations of MFS are most frequently caused by substitutions for cysteine in precursor transforming growth factor β (TGF-β) like domains in fibrillin-1 [Dietz and Pyeritz, 1995]. A similar pattern is beginning to emerge for fibrillin-2 mutations in CCA. Four fibrillin-2 mutations reported to date (including here), that cause classic CCA, are cysteine substitutions. It is also of interest that all reported FBN2 mutations occur in the longest stretch of TGF-β like domains, the region homologous to the "neonatal region" of FBN1 [Wang et al., 1996; Putnam et al., 1995; Kainulainen et al., 1994]. This observation suggests that mutations in a limited region of FBN2 cause the CCA phenotype. Thus, it is possible that mutations in other regions of FBN2 cause phenotypes that are not reminiscent of a "Marfan-like" disease.

The phenotype of patient CF1347 was typical for CCA and her cysteine substitution occurred in exon 26. Patient CF1449 had a more unusual clinical course. Her mild developmental delay is probably unrelated to the mutation in fibrillin-2. It is of interest that substitution of this cysteine (position 1252) had already been described by Putnam et al. [1995]. However, in that case the substitution was a tyrosine residue.

Finally, we found a 3′ UTR polymorphism in patient CF1347 and several other patient and controls. The frequency of this polymorphism in our population is 6.0%. Studies in MFS have shown that individuals with relatively mild disease have a decreased expression of the mutant FBN1 allele when compared to the wild-type allele in the same patient. Initial research in CCA indicated that the mutant allele was expressed at levels higher than the wild-type allele [Putnam et al., 1997]. Therefore, we took advantage of this polymorphism to examine the expression of the normal and mutant FBN2 alleles of patient CF1347. We found equal steady-state expression of both normal and mutant alleles in cultured fibroblasts (data not shown). This finding is similar to what is seen in patients with classic MFS having FBN1 mutations [Karttunen et al., 1996].

Exon skipping has been seen in about one third of the cases of CCA. This rate is much greater than the observed rate of mis-splicing in FBN1. In addition, instances of somatic and germline mosaicism have been documented [Putnam et al., 1997; Wang et al., 1996]. This too appears rather high, given the relatively small number of patients. The reasons for these observations and the variability in expression of mutant versus wild-type alleles [Babcock et al., 1998; Park et al., 1998; Putnam et al., 1997] are unclear. Further studies in more patients and the availability of animal models will facilitate the understanding of fibrillin-2 pathogenesis.

ACKNOWLEDGMENTS

M.G. is an Established Investigator of the American Heart Association (funding was contributed in part by the AHA Florida Affiliate). The expert graphics assistance of Mr. Joe Edwards is greatly appreciated.

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